Risk Assessment for Carcinogens: A Comparison of Approaches of the ACGIH and the EPA

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The relative carcinogenic potency of 16 chemicals evaluated by both the U.S. Environmental Protection Agency (EPA) and the Chemical Substances Threshold Limit Values (CS-TLV) Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) were compared. The estimated cancer risk resulting from occupational exposure to the threshold limit values (TLVs) were also computed using dose–response curves developed as a part of EPA quantitative risk assessments.

Substantial agreement between the EPA and the CS-TLV Committee was found when the relative potency of these carcinogens was compared. Use of EPA's risk model to estimate lifetime cancer risk from occupational exposure at the TLV levels often resulted in high cancer risk estimates. The approaches used to assess cancer risk by both groups is described and a suggestion is made for incorporating existing quantitative risk assessments into the TLV evaluation procedure. **Alavanja, M.C.R.; Brown, C.; Spirtas, R.; Gomez, M.: Risk Assessment for Carcinogens: A Comparison of Approaches of the ACGIH and the EPA. Appl. Occup. Environ. Hyg. 5:510–517; 1990.**

Introduction

The Chemical Substances Threshold Limit Values (CS-TLV) Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) has been reviewing its policies and procedures regarding carcinogens. Spirtas *et al.* (1985) described the current process the CS-TLV Committee uses to make the qualitative decision to designate a chemical as a workplace carcinogen and the quantitative decision to recommend levels of exposure for the guidance of industrial hygienists.(1) Threshold limit values (TLVs) (for carcinogens as well as other toxic agents) are time-weighted averages (TWAs) for a normal 8-hour workday, 40-hour workweek. The TLV is set for inhalation exposure, with special notifications for agents where absorption from skin exposure is important. The TLV is assumed to be protective for "nearly all workers" assuming the workers to be healthy adults.(1) TLVs are guidelines for good work practices to be used only by professional industrial hygienists. For substances which cause chronic diseases such as cancer, however, there may not be a sharp cutoff point (threshold) between effect and no effect; it is, therefore, important that professional judgment be used in monitoring and protecting workers exposed to such substances.

When deciding on guidelines for carcinogens, the CS-TLV Committee gives greatest weight to epidemiologic studies having data on quantitative exposure levels.(1) Such substances receive an A1 categorization and are called "Confirmed Human Carcinogens." Next in importance, and more typically available, are mammalian toxicologic studies having whole-body bioassays. Such substances are given an A2 designation and are called "Suspected Human Carcinogens." In reviewing the key experimental toxicology studies, the Committee considers route of entry (greatest weight given to inhalation studies), dose–response gradient, potency, mechanism of action, cancer site, time-to-tumor, length of exposure, and underlying incidence rate for the type of cancer and species under study. Replication of results is important, especially if comparable in different species. Other types of studies are useful in confirming

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that a substance is a carcinogen but are not usually helpful in setting a TLV. A safety factor is often applied to establish a TLV for carcinogens, by taking the lowest level known to induce cancer (or the no-effect level) and then dividing that by an arbitrary factor, such as 10 or 100. The CS-TLV Committee, realizing the imprecision of setting TLVs for carcinogens, recommends that, for all carcinogens having a TLV, "worker exposure by all routes should be carefully controlled to levels as low as reasonably achievable (ALARA) below the TLV."[2]

In the early 1970s, the U.S. Environmental Protection Agency (EPA) developed an approach that was different from that of the CS-TLV Committee. Early decisions by the EPA conveyed the idea that the only acceptable degree of regulation of carcinogens would be a total ban on exposures.[3,4] However, the impracticality of achieving zero risk on a broad scale for a large number of economically important chemicals became increasingly apparent to many, including the U.S. Congress. As a result, the EPA in 1976 became the first federal agency to adopt formal guidelines embracing a two-step process of risk assessment. The first step is a determination of whether a particular substance constitutes a cancer risk, i.e., hazard identification. The second step includes a quantitative risk assessment (QRA) as a key component of determining the degree of regulatory action needed to protect the public.[5]

As part of the QRA process, the EPA computes dose–response curves, makes low-dose extrapolations, and estimates the size and degree of exposure of the exposed populations in order to estimate the number of excess cancers expected in the total U.S. population. The rationale and procedures for the EPA approach are used to guide regulatory actions which are meant to protect each member of the general public over a lifetime against exposure via inhalation or ingestion.[6] Regulatory action is taken only after the results of the QRA are integrated with engineering data and with social, economic, and political concerns.[7]

Confusion has arisen from the different approaches used by the CS-TLV Committee and the EPA in estimating risk. Although the TLVs continue to be used widely by professional industrial hygienists around the world to evaluate the safety of workplace exposures, the QRA approach is viewed by some as more objective. Recently, criticism of TLVs has focused attention on the objectivity and scientific standards of the CS-TLV Committee.[8] Several examples were given of chemical substances for which unpublished data (primarily from the files of industrial companies) were important in setting the recommended TLV. Since, in many instances, the TLV is the only number available to industrial hygienists, it is important that the CS-TLV Committee's policies and procedures regarding carcinogens be reviewed to assess the results of the current TLV approach. We believe a quantitative comparison of the EPA and the TLV approaches may provide some important information regarding this assessment.

Reflecting on some of these issues, Andersen[9] presented a critical review of quantitative risk assessment in occupational health in the 1988 Herbert E. Stokinger Lecture, concluding that, "Quantitative Risk Assessment is not just coming to the occupational environment. It is here now and is an issue to be reckoned with by everyone of us in the industrial hygiene profession."[9] In his review, Andersen suggests that QRA during the past 13 years has been "damned" by its misapplication. Overly conservative quantitative approaches to predicting risk would lead to risk estimates that "greatly restrict commercial operations, decrease our ability to compete in world markets, and lead to large expenditures to change work practices with no concomitant increase in health protection." He went on to suggest that the problems faced by the use of overly conservative techniques can be overcome in part by the use of recent cancer models that have greater biological relevance, e.g., the physiologically based pharmacokinetics models (PB-PK)[10] and the Moolgavkar, Venzon, Knudson (MVK) models.[11] Although the theoretical appeal of these cancer models is clear, the bulk of the QRAs developed and published since 1976 have come from regulatory agencies which have not used these new techniques. We cannot compare current TLVs to the results of risk assessments using the MVK or PB-PK approaches; however, comparing established TLVs for carcinogens with the results of the EPA QRAs may help determine whether, and under what circumstances, the CS-TLV Committee may consider using QRAs as part of its decision-making process. This article presents a comparison between the ACGIH TLVs and the EPA QRAs for the 16 chemical carcinogens that have been evaluated by both groups. These QRAs were chosen for comparison since they are the largest available collection of risk assessments developed by a standard methodologic approach.

Methods and Results

The comparison reported here is derived from the ACGIH 1988–1989 list of TLVs[12] and an EPA list of carcinogens taken from the Integrated Risk Information System.[13] The ACGIH list contains over 700 agents of which 55 are classified by the Committee as carcinogens in the adopted list plus 3 in the Notice of Intended Changes List. These 55 substances are listed along with their TLVs, where available, in Table I. The EPA list, in Table II, contains 54 agents, including a substantial number of pesticides and nitrosamines for which a unit risk factor for inhalation exposure is available. The EPA's unit risk factor is a conservatively estimated risk to humans from constant lifetime exposure of breathing contaminated air at a level of 1 $\mu g/m^3$. This risk estimate is derived from the available results of animal bioassays, biochemical studies, and epidemiologic studies. To assure safety, conservative assumptions are used to supplement missing or unknown information (e.g., using results from the most sensitive animal species and the linearized multistage dose–response model and extrapolating using the upper 95 percent confidence limit of the experimental evidence).

The ACGIH TLVs are compared with the EPA QRAs

TABLE I. Chemical Substances Classified as Carcinogens by ACGIH with Their Respective TLVs (1988–1989 Adopted Values)

Substance	TLV	Substance	TLV
Acrylamide—Skin[A]	0.03 mg/m^3	Ethylene dibromide—Skin	—
Acrylonitrile—Skin[A]	4.5 mg/m^3	Ethylene oxide[A]	1.8 mg/m^3
4-Aminodiphynyl—Skin	—[B]	Formaldehyde[A]	1.5 mg/m^3
Antimony trioxide production	—	Hexachlorobutadiene—Skin[A]	0.21 mg/m^3
Arsenic trioxide production	—	Hexamethyl phosphoramide—Skin	—
Asbestos		Hydrazine—Skin	0.13 mg/m^3
Amosite	0.5 fiber/cc	4,4′-Methylene bis(2-chloroaniline)—Skin	0.22 mg/m^3
Chrysotile	2 fibers/cc	Methylene chloride (Dichloromethane)[A]	175 mg/m^3
Crocidolite	0.2 fiber/cc	4,4′-Methylene dianiline	0.81 mg/m^3
Other forms	2 fibers/cc	Methyl hydrazine—Skin	0.35 mg/m^3
Benzene[A]	32 mg/m^3	Methyl iodide—Skin	12 mg/m^3
Benzidine—Skin	—[B]	β-Naphthylamine	—[B]
Benzo(a)pyrene	—	Nickel sulfide roasting, fume & dust	1 mg/m^3, as Ni
Beryllium[A]	0.002 mg/m^3	4-Nitrodiphenyl	—[B]
1,3-Butadiene[A]	22 mg/m^3	2-Nitropropane	35 mg/m^3
Carbon tetrachloride—Skin[A]	31 mg/m^3	N-Nitrosodimethylamine—Skin	—
Chloroform[A]	49 mg/m^3	N-Phenyl-beta-naphthylamine	—
bis-(Chloromethyl)ether[A]	0.005 mg/m^3	Phenylhydrazine—Skin	22 mg/m^3
Chlormethyl methyl ether	—	Propane sultone	—
Chromates of lead, as Cr	0.05 mg/m^3	β-Propiolactone	1.5 mg/m^3
Chromite ore processing (chromate)	0.05 mg/m^3, as Cr	Propylene imine—Skin	4.7 mg/m^3
Chromium (Vi), certain water insoluble compounds[A]	0.05 mg/m^3, as Cr	o-Tolidine—Skin	—
Chrysene	—	o-Toluidine—Skin	9 mg/m^3
Coal tar pitch volatiles	0.2 mg/m^3, as benzene solubles	p-Toluidine—Skin	9 mg/m^3
		Vinyl bromide	22 mg/m^3
3,3′-Dichlorobenzidine—Skin	—	Vinyl chloride	13 mg/m^3
Dimethyl carbamoyl chloride	—	Vinyl cyclohexene dioxide—Skin	57 mg/m^3
1,1-Dimethylhydrazine—Skin	1.2 mg/m^3	Zinc chromates	0.01 mg/m^3, as Cr
Dimethyl sulfate—Skin	0.5 mg/m^3		

Notice of Intended Changes (for 1988–1989)

Cadmium and compounds[A]	0.1 mg/m^3	Ethyl acrylate	20 mg/m^3	Xylidine (mixed isomers)—Skin	2.5 mg/m^3

[A]Chemicals contained on both the TLV and EPA carcinogen list.
[B]Substance designed by CS-TLV Committee as a confirmed human carcinogen without a TLV. Workers exposed to this substance should be "properly equipped to virtually eliminate all exposure."[2]

in two ways: 1) do the ACGIH and EPA place these chemicals in the same order of toxicity? and 2) what level of risk do the EPA unit risk factors imply from exposure to the ACGIH's TLVs? The EPA dose–response assessment commonly begins with the multistage model,

$$P(d) = 1 - \exp(q_1 d + q_2 d^2 + \ldots + q_k d^k),$$

puts an upper 95 percent confidence limit on the linear term of the dose–response (q_1^*) based on a statistical evaluation of animal bioassay data (with consideration of species, route of administration, duration of exposure and followup, and other experimental design criteria deemed most relevant to human risk assessment), and then uses the linearized multistage model (only the linear term is included) to estimate the risk of lifetime exposure to low doses. Because the linearized multistage model used by the EPA for its unit risk factor is equivalent to the single hit model, our estimate of lifetime risk of developing cancer from occupational exposure is based on the model,

$$\text{Prob}(d) = 1 - \exp(-\alpha d),$$

where Prob(d) is the lifetime probability of developing cancer from exposure to a daily level of d $\mu g/m^3$ during a working lifetime of a 40-hour workweek/168-hour week, a 50-week/workyear, a 40-year career, and an average life span of 74 years. The slope of this dose–response curve (α) directly indicates cancer risk, thus a larger slope implies a larger risk at the same dose. The slope is derived from the EPA unit risk factor and is adjusted as follows to reflect different exposure situations.

To adjust for different exposure durations, we use the simple assumption that the dose–response slope for occupational exposure is $(40/168) \times (50/52) \times (40/74) = 0.124$ of the complete lifetime exposure slope. The EPA assumes a normal respiration rate of 20 cubic meters in a 24-hour period while we assume a rate of 10 cubic meters in an 8-hour working day. Therefore, to adjust for different breathing rates for working and nonworking persons, we assume the occupational exposure slope is $(10/8)/(20/24) = 1.5$ times the EPA slope.

Figure 1 displays the comparison of the ACGIH and EPA arrangements of the 16 common agents in decreasing order of risk (increasing TLV level and decreasing unit risk order). The spearman rank correlation coefficient for these two orderings is $r = 0.78$ implying substantial, yet imperfect, agreement. The major disagreements are the orderings of hexachlorobutadiene, 1,3-butadiene, vinyl chloride, formaldehyde, and chloroform. The ACGIH has hexachlorobutadiene with a greater carcinogenic risk than 1,3-butadiene, and vinyl chloride with a greater risk than

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chloroform, while the EPA reverses this order. In addition, formaldehyde is substantially higher on the ordering by ACGIH than by EPA. In establishing TLVs for vinyl chloride and chloroform, the CS-TLV Committee probably weighted heavily the positive epidemiologic evidence for vinyl chloride, in deciding to establish a relatively more protective value for vinyl chloride than for chloroform. The TLV for formaldehyde is based primarily on prevention of eye, nose, and throat irritation. These acute effects have been observed in humans at levels below the lowest effect seen for carcinogenicity in rodents. The discrepancy for 1,3-butadiene can be explained, in part, by the CS–TLV Committee minimizing the relevance of an animal bioassay which induced angiosarcomas of the heart, a rare tumor in humans.

Table III gives the TLVs and adjusted unit risk for these agents along with the EPA's estimate of daily occupational exposure levels corresponding to lifetime cancer risks of one in a million and one in a thousand. This table also gives an estimate of the lifetime risk from occupational exposure to a daily level at the TLV. Eight of these 16 estimated lifetime cancer risks from occupational exposure to the TLV lie between 1 and 10 percent with the two highest estimates being chloroform at 19 percent and 1,3-butadiene at 68 percent while the two lowest estimates are hexachlorobutadiene at 0.1 percent and beryllium at 0.09 percent. On the average, the TLVs for these 16 agents are over 25 times greater than the EPA estimated daily exposure level associated with a risk of 1/1000. Table III also

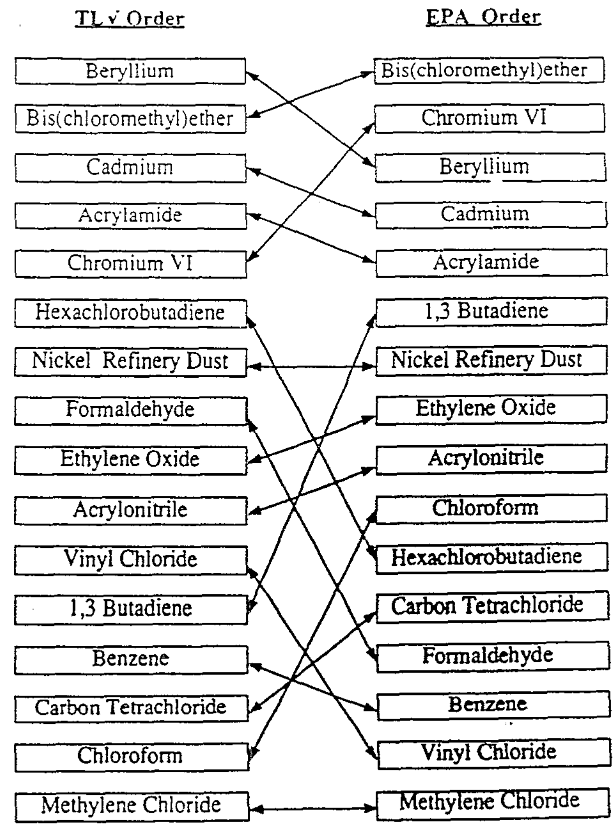

FIGURE 1. Ordering of chemicals by estimated risk by the Chemical Substances TLV Committee and the U.S. Environmental Protection Agency.

TABLE II. Chemicals Carcinogens for Which Quantitative Risks Have Been Computed for Inhalation Exposure by U.S. EPA's Carcinogen Assessment Group

Compounds	Unit Risk Factors*	Compounds	Unit Risk Factors*
Acetaldehyde	2.2×10^{-6}	1,2-Diphenylhydrazine	4.5×10^{-1}
Acrylamide	1.3×10^{-3}	Epichlorohydrin	1.2×10^{-6}
Acrylonitrile	6.8×10^{-5}	Ethylene oxide	1.8×10^{-2}
Aldrin	4.9×10^{-3}	Formaldehyde	1.1×10^{-4}
Arsenic	4.3×10^{-3}	Heptachlor	1.3×10^{-3}
Asbestos	2.3×10^{-1}	Haptachlor epoxide	2.6×10^{-3}
Azobenzene	3.1×10^{-5}	Hexachlorobutadiene	2.2×10^{-5}
Benzene	8.3×10^{-6}	Hexachlorocyclohexane	2.1×10^{-5}
Benzidene	6.7×10^{-2}	technical grade	2.0×10^{-1}
Beryllium	2.4×10^{-3}	alpha isomer	1.8×10^{-3}
1,3-Butadiene	2.8×10^{-4}	beta isomer	5.3×10^{-4}
Cadmium	1.8×10^{-3}	Hexachlorodibenzodioxin	1.3×10^{-6}
Carbon tetrachloride	1.5×10^{-5}	Hydrazine/Hydrazine sulfate	4.9×10^{-3}
Chlordane	3.7×10^{-5}	Nickel refinery dust	2.4×10^{-4}
bis(2-chloroethyl)ether	3.3×10^{-4}	Nickel subsulfide	4.8×10^{-4}
Chloroform	2.3×10^{-5}	Nitroso-dimethylamine	1.4×10^{-2}
bis(chloromethyl)ether	6.2×10^{-2}	Di-butylamine	1.6×10^{-3}
Chromium VI	1.2×10^{-2}	Diethylnitrosamine	4.3×10^{-2}
DDT	9.7×10^{-5}	N-nitrosopyrrolidine	6.1×10^{-4}
1,2-Dibromoethane	2.2×10^{-4}	1,1,1,2-Tetrachloroethane	7.4×10^{-6}
Dibutylnitrosamine	1.6×10^{-3}	1,1,2,2-Tetrachloroethane	5.8×10^{-5}
1,2-Dichloroethane	2.6×10^{-6}	Toxaphene	3.2×10^{-4}
1,1-Dichloroethylene (Vinylidene chloride)	5.0×10^{-5}	1,1,2-Trichloroethane	1.6×10^{-5}
Dichloromethane (Methylene chloride)	4.1×10^{-6}	Trichloroethylene	1.3×10^{-6}
Dieldrin	4.6×10^{-3}	2,4,6-Trichlorophenol	5.7×10^{-6}
Diethylnitrosamine	4.3×10^{-2}	Vinyl chloride	7.1×10^{-6}
Dimethylnitrosamine	1.4×10^{-2}		

*Estimated risk to humans from constant lifetime exposure of breathing contaminated air at a level of 1 $\mu g/m^3$.

TABLE III. Estimated Lifetime Cancer Risk from Occupational Exposure to the TLV

Substance	IARC Class	TLV $\mu g/m^3$	Adjusted Unit Risk*	Daily Exposure ($\mu g/m^3$) Associated with Risk of 1/10^6	1/10^3	Estimated Lifetime Cancer Risk from Exposure to TLV
Acrylamide	2B	30	2.4×10^{-4}	4.2×10^{-3}	4.2	0.0072
Acrylonitrile	2A	4500	1.3×10^{-5}	7.7×10^{-2}	7.7×10^{1}	0.057
Benzene	1	30000	1.5×10^{-6}	6.7×10^{-1}	6.7×10^{2}	0.044
Beryllium	2A	2	4.5×10^{-4}	2.2×10^{-1}	2.2	0.0009
1,3-Butadiene	2B	22000	5.2×10^{-5}	1.9×10^{-2}	1.9×10^{1}	0.68
Cadmium	2A	10	3.3×10^{-4}	3.0×10^{-3}	3.0	0.0033
Carbon tetrachloride	2B	30000	2.8×10^{-6}	3.6×10^{-1}	3.6×10^{2}	0.081
Chloroform	2B	50000	4.3×10^{-6}	2.3×10^{-1}	2.3×10^{2}	0.19
bis(chloromethyl)ether	1	5	1.2×10^{-2}	8.3×10^{-5}	8.3×10^{-2}	0.058
Chromium (VI)	1	50	2.2×10^{-3}	4.5×10^{-4}	4.5×10^{-1}	0.10
Dichloromethane (Methylene chloride)	2B	175000	7.6×10^{-7}	1.3	1.3×10^{3}	0.12
Ethylene oxide	2A	2000	2.0×10^{-5}	5.0×10^{-2}	5.0×10^{1}	0.039
Formaldehyde	2A	1500	2.4×10^{-6}	4.2×10^{-1}	4.2×10^{2}	0.0036
Hexachlorobutadiene	3	240	4.1×10^{-6}	2.4×10^{-1}	2.4×10^{2}	0.00098
Nickel refinery dust	1	1000	4.5×10^{-5}	2.2×10^{-2}	2.2×10^{1}	0.044
Vinyl chloride	1	10000	1.3×10^{-6}	7.7×10^{-1}	7.7×10^{2}	0.013

*From Table II adjusted for occupational exposure. Estimated risk to humans from exposure to a time-weighted average of 1 $\mu g/m^3$ for a normal 8-hour workday, 40-hour workweek, 40-year career (see text).

contains the International Agency for Research on Cancer's (IARC) classification of each of these chemicals.[14] This classification scheme evaluates the likelihood that these chemicals are human carcinogens but makes no attempt to quantify their potential risk or to set "safe" exposure levels. Hexachlorobutadiene is classified by IARC in category 3, "the agent is not classifiable as to its carcinogenicity to humans."[14] Seven other chemicals: acrylamide (2B), acrylonitrile (2A), beryllium (2A), 1,3-butadiene (2B), cadmium (2A), carbon tetrachloride (2B), chloroform (2B), methylene chloride (dichloromethane) (2B), ethylene oxide (2A), and formaldehyde (2A) are in IARC category 2, "the agent is probably (2A) or possibly (2B) carcinogenic to humans." The remaining five chemicals, benzene, bis(chloromethyl) ether, chromium VI, nickel refinery dust (nickel compounds), and vinyl chloride are in IARC category 1 "human carcinogens."

Using vinyl chloride as an example, Figure 2 illustrates the typical relationship found between the dose–response curve resulting from a QRA of the type performed by the EPA, the empirical data on which the modeling is performed, and the TLV established by the ACGIH. The slope of the dose–response curve shown here (i.e., 0.0013) is derived from the EPA unit risk factor for vinyl chloride adjusted to reflect the exposure situation of the occupational environment.

Discussion

In this set of 16 chemicals, both the EPA and the ACGIH approaches rank them in approximately the same order of carcinogenic risk. However, the EPA is far more conservative, reflecting the agency's objective to protect all members of the community, not just healthy adults. The authors could not definitively comment on the relative accuracy of the two approaches because our theoretical understanding of the dose–response relationship for occupational carcinogens is still elementary, and we are, therefore, limited in our ability to discriminate between the accuracy of the TLV and QRA approaches. One is further hampered by the fact that the empirical data available to assess the carcinogenicity of specific chemicals are usually the result of animal experiments at high doses, together with a battery of short-term tests which are sometimes augmented by epidemiology studies that usually have scanty exposure information. The available occupational cohort studies have not followed workers for their entire lifetime and, thus, do not give complete information on agents which cause cancer many years after exposure. Consequently, no one at the present time can speak with scientific certainty about "safe" levels of exposure to carcinogens.

Although decisions on the permissible exposure to carcinogens are fraught with difficulty, we believe that recommending maximum levels of occupational exposure should be guided by three principles:

1. Scientifically, one should seek the most appropriate data and methods for predicting the effect of human exposure to carcinogens based on our latest theoretical understanding of the process of carcinogenesis.
2. As a public health issue, one should admit the imprecision of our knowledge and compensate for our uncertainty by building into the system a margin of safety.
3. As public policy, one should explicitly document the methodology.

The increasing motivation to use QRA as a tool to establish occupational health standards dates from the 1980 decision by the Supreme Court to overturn the Occupational Safety and Health Administration's (OSHA) newly proposed benzene standard.[15] The court maintained that

OSHA had failed to show a significant reduction in risk going from 10 to 1 ppm. Although OSHA did not propose a formal policy in response to the decision, the agency has generally accepted the view that quantitation of risk is required for the regulation of carcinogens, and it has incorporated QRAs into its standard setting activity since that time.

Amidst the controversy associated with modeling a process that is incompletely understood scientifically and the judicial political climate which favors the use of a quantitative procedure to help regulate carcinogens in the general environment and workplace, the EPA and other regulatory agencies have opted for the use of a conservative approach in the development of risk assessment procedures. For example, the QRAs are usually based on the most sensitive species and use of the most conservative dose–response curve, while low weight is given to negative epidemiological data.[5] Although this procedure has been criticized by some industry representatives[16] and some academic scientists,[17] it would be difficult to perform numerous risk calculations involving all plausible options for the many judgments that must be made in the development of a QRA. For most chemicals, this would result in such a wide range of risk estimates that the analysis would not be useful to the regulatory agency or to others formulating public policy. The CS-TLV Committee, on the other hand, provides recommendations for the use of industrial hygienists rather than setting governmental standards, and the Committee bases its recommendation on the professional judgement of its members. Both the TLVs and QRAs are subject to external reviews before adoption.

With this perspective in mind, the authors compared the chemical carcinogens which were quantitatively evaluated by the two procedures. The first qualitative comparison is that only 16 chemicals appear on both the CS-TLV Committee list and the EPA list. However, this apparent disagreement is not too surprising because of the substantially different mission of these two organizations and the approaches they take when classifying the hazardous "potency" of chemicals. TLVs are quantitative guidelines for recommended exposures in the workplace, but there is no explicit estimate of the health risk associated with these levels. On the other hand, the EPA unit risk factor explicitly relates dose to cancer risk by means of a mathematical, linearized, multistage model of carcinogenesis, but few have been translated into permissible exposure levels. Operating as an independent organization, the IARC reviews all relevant scientific information in order to assess the evidence that an agent could alter the incidence of cancer in humans but makes no attempt to extrapolate beyond the range of the available data. Likewise, no recommendation is given for safe exposure levels for regulation or legislation.[14]

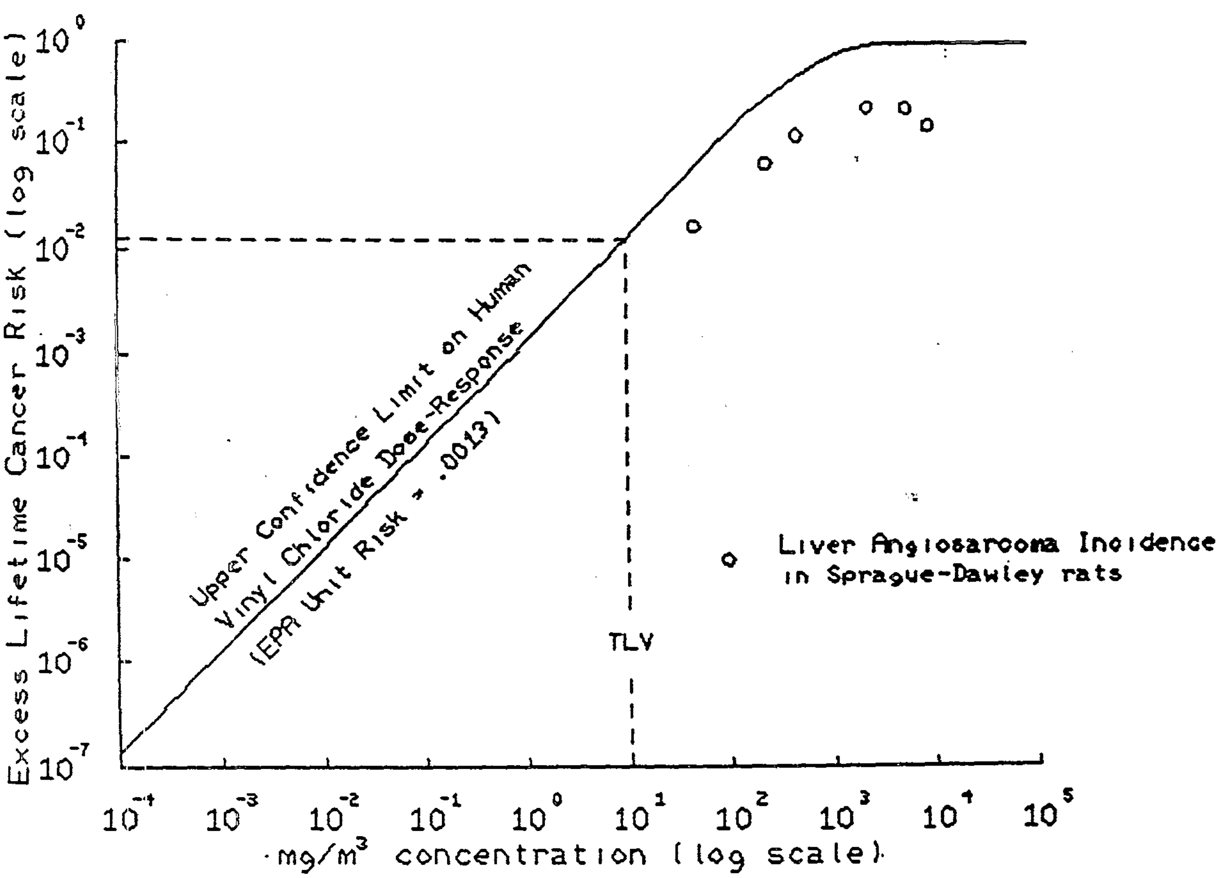

FIGURE 2. Comparison of TLV, EPA unit risk dose-response, and animal bioassay results for vinyl chloride exposure.

The principal reason for this wide disparity between the EPA and the CS-TLV Committee may be explained primarily by the underlying philosophical principles governing the two organizations rather than the technical differences between the two methods. The CS-TLV Committee is governed by the principle that "Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. Because of wide variation in individual susceptibility, however, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit; a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness."[12] Use of the TLV for other purposes, such as community air standards, is specifically discouraged by the Committee. Thus, the CS-TLV Committee recommendations imply that there is a small degree of risk of occupational illness to some workers who are more susceptible than others.

The Clean Air Act, which in part governs EPA's approach to performing QRAs, is more philosophically conservative. The Act states that Primary Air Standards must protect the public health with an adequate margin of safety based on a review of air quality criteria which reflects the latest state of scientific knowledge about the pollutant. The requirement for an "adequate margin of safety" is intended both to address inconclusive scientific and technical information and to provide a reasonable degree of protection against hazards that research has not yet identified. Recognizing that imposing zero emission for some substances would impose too heavy an economic burden on society, EPA has addressed the problem by proposing that the Best Available Technology (BAT) be used to control carcinogens. If BAT controls leave an unreasonable residual risk, further controls will be considered.[17]

When making a quantitative comparison between the ACGIH and the EPA approaches, substantial agreement is found when classifying the relative potencies of these carcinogens, but substantial disparity in the actual levels proposed or recommended. Estimating lifetime cancer risks from occupational exposure at the ACGIH's TLV levels by using the EPA's QRA model sometimes resulted in extraordinarily high risk estimates, 68 percent from exposure to 1,3-butadiene and 19 percent from exposure to chloroform, which may reflect either limitations in the QRA modeling approach or the TLV safety factor approach.

A safety factor approach, such as that used by the CS-TLV Committee, is theoretically no more or less conservative than a QRA approach which is linear at low doses and assumes no threshold. In practice, however, use of a safety factor of 5–10 or even 100–1000 is markedly less conservative than the QRA approach which determines an exposure level associated with a very small risk level such as $1/10^6$. This point is illustrated for vinyl chloride in Figure 2 which compares the EPA unit risk factor for the upper confidence limit on the estimated human dose–response with the TLV and the results of animal bioassays. With no attempt made to acknowledge the inconsistency produced by these differing methods, confusion and skepticism have resulted. Although there are strengths and weaknesses associated with the approach of each group, it would seem that the CS-TLV Committee could make a major contribution to fostering control of carcinogens in the workplace by reviewing any available EPA QRA, or comparable modeling data when it updates or establishes a new TLV for a confirmed or suspected human carcinogen. When possible, the CS-TLV Committee should also consider the results of studies that use more refined models for QRA. Being less constrained by the judicial–political climate than the regulatory agencies, the CS-TLV Committee should be better able to promptly adopt the most scientifically defensible extrapolation procedures available when a particular chemical is being studied in terms of recommended occupational exposure values.

Although many scientists remain skeptical about the possibility of extrapolating the effects of carcinogens to low doses, a systematic evaluation of the results of these estimates in future editions of the TLV Documentation volume would help alleviate the confusion that now exists.

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